Prophylactic role of ivermectin in SARS-CoV-2 infection among healthcare workers

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Abstract

Background Healthcare workers (HCWs) are vulnerable to getting infected withSARS-CoV-2. Preventing HCWs from getting infected is a priority to maintain healthcare services. The therapeutic and preventive role of ivermectin in COVID-19 is being investigated. Based on promising results of in vitro studies of oral ivermectin, this study was conducted with the aim to demonstrate the prophylactic role of oral ivermectin in preventing SARS-CoV-2 infectionamong HCWs at All India Institute of Medical Sciences (AIIMS), Bhubaneswar.

Methods A prospective cohort study was conducted at AIIMS Bhubaneswar, which provides both COVID and Non-COVID care since March 2020. All employees and students of the institute who provided written informed consent participated in the study.Uptake of two-doses of oral ivermectin (300 µg/kg at a gap of 72 hours) was considered as exposure. The primary outcome of the study was COVID-19 infection in the following month of ivermectin consumption diagnosed by RTPCR as per Government of India testing criteria guidelines.The log-binomial model was used to estimate adjusted relative risk, and the Kaplan-Meier failure plot was used to estimate the probability of COVID-19 infection with follow-up time.

Results Of 3892 employees, 3532 (90.8%) participated in the study. The ivermectin uptake was 62.5% and 5.3% for two-doses and single-dose, respectively. Participants who took ivermectin prophylaxis had a lower risk of getting symptoms suggestive of SARS-CoV-2 infection(6% vs 15%). HCWs who had taken two-doses of oral ivermectin have a significantly lower risk of contracting COVID-19 disease during the following month (ARR 0.17; 95% CI, 0.12-0.23). Females had a lower risk of contracting COVID-19 than males (ARR 0.70 95% CI, 0.52-0.93). The absolute risk reduction of SARS-CoV-2 infection was 9.7%. Only 1.8% of the participants reported adverse events, which were mild and self-limiting.

Conclusion and relevance Two-doses of oral ivermectin (300 µg/kg given 72 hours apart) as chemoprophylaxis among HCWs reduces the risk of COVID-19 infection by 83% in the following month. Safe, effective, and low-cost chemoprophylaxis have relevance in the containment of pandemic alongside vaccine.

Introduction

The COVID-19 pandemic that started as an outbreak in Wuhan, Hubei Province of China in December 2019 has affected around 50 million people and caused the death of approximately 1.2 million people in 11 months.[1]In India, about 8.5 million people have suffered, and 126000 people have died due to this disease.[2] Although healthcare workers (HCWs) represent less than 3% of the population in the large majority of countries and less than 2% in almost all low- and middle-income countries, around 14% of COVID-19 cases reported to the World Health Organization (WHO) are among HCWs,[3] with the proportion reaching as high as 35% in some countries.[3] HCWs are more vulnerable to infection due to the very nature of their occupation, and ensuring their safety is of paramount importance in a functioning health system.

Therefore, prevention of COVID-19 disease among HCWsis a priority for all administrators and governments.

Despite the high advocacy on behavioural prophylaxis since the start of the pandemic, cases and deaths keep on increasing, indicating that only behavioural prophylaxis may not be enough to control the COVID-19 pandemic. In addition to behavioural prophylaxis, there is a need for an alternate safe intervention that can provide protection against COVID-19.To date, there is no effective cure or vaccine available to treat or protect people.[4] The beneficial role of ivermectin in the prevention, as well as treatment of COVID-19, has been explored in the recent past.[5,6,7,8] The well-known *in vitro* study by Caly et al., observational studies, and an open-label randomized controlled trial conducted so far have suggested the potential role of ivermectin as chemoprophylaxis for prevention of COVID-19.[5,6,7,8]We noticed an increasing number of HCWs getting infected withSARS-CoV-2 infectionin early September 2020 at our hospital, which was negatively impacting on the healthcare services we had to provide. After carefully assessing the published information on ivermectin, we decided to investigate the role of ivermectin prophylaxis in the prevention of COVID-19 among HCWs following one month of administration in our hospital, which is a tertiary care teaching hospital in Eastern India.

Methods

Aim

To demonstrate the prophylactic role of oral ivermectin in preventing SARS-CoV-2 infectionamong HCWs at All India Institute of Medical Sciences (AIIMS), Bhubaneswar.

Design

A prospective cohort study

Study Setting

The study was conducted at the All India Institute of Medical Sciences (AIIMS), Bhubaneswar, India, during September-November 2020.

Study cohort

All staff members of the institute formed the study cohort, which included the clinical staff engaged in inpatient care activities, administrative staff, and students. Written informed consent was obtained from all participants for inclusion in the study. Telephonic data collection was done from all study participants using administrative records.The study participants were recruited from 20/09/2020 to 30/09/2020, followed up after one month of taking oral ivermectin from 20/10/2020 to 30/10/2020 to assess the outcome.

Exposure and Outcome

Based on a consensus statement prepared by experts from the various departments of the hospital, on September 17, 2020, a decision was taken to provide a prophylactic dose of oral ivermectin to HCWs and students. [Panel 1] The consensus statement recommended and approved a regimen of 300 µg/kg body weight with the first two doses taken 72 hours apart, followed by a once-monthly dose on the 30th day from the last dose. Ivermectin was made available free of cost to the HCWs. Intake of two-doses of oral ivermectin (300 µg/kg at a gap of 72 hours) was considered as exposure. The outcome was defined as a confirmed case of COVID-19 detected by RT-PCR. Healthcare workers were tested followingthe Government of India testing strategy for COVID-19 at the institute.[9] Furthermore, the HCWs were followed-up through telephonic calls to confirm their COVID-19 status after a month of distribution of ivermectin prophylaxis.

Statistical analysis

Statistical analysis was done using STATA 13.0 software. Themean and standard deviation was reported for continuous variables and proportions for categorical variables. The log-binomial model was used to estimate adjusted relative risk.[10] We also performed a sensitivity analysis, excluding those who were COVID-19 positive before the ivermectin prophylaxis.

Kaplan-Meier failure plot was used to estimate the probability of SARS-CoV-2 infectionwith follow-up time.

Ethical consideration

The protocol was approved by the Institutional Ethics Committee of AIIMS Bhubaneswar (T/IM-NF/CM&FM/20/142). Written informed consent was obtained from each participant. Efforts were taken to maintain the anonymity of the participants throughout the process. COVID19 positive HCWs and students during the study period were treated at the institute.

Results

The institute was functioning with 3892 members during September 2020. Out of 3892, 262 were excluded from the study as they did not consent to participate in the study. Another 98 participants couldnot be followed up and were excluded from the study. A total of 3532 participants were included in the study. The mean (SD) age was 30.6(8.6) years. Over half of the study participants were less than 30 years (53.4%), while one-third (32.3%) were in the 30 to 39 years age group. The majority of participants were male (67.6%). Approximately three-fourths (72.7%) of the participants were involved in the direct management of COVID-19 patients. Administrative staff and students comprised 13.9% and 13.4%, respectively. Among the 2567 participants, who were involved in COVID-19 patient care, 812 were doctors, 717 were nursing officers, and 1038 were supporting staff. [Table 1]

Uptake of ivermectin was 67.5% (62.2% two-doses and 5.3% single-dose). Rest 1147 (32.5%) participants did not consume ivermectin as prophylaxis. The symptoms suggestive of SARS-CoV-2 infection(as per

WHO guideline),[11]were present among 331 (9.4%) participants during one-month follow-up. A total of 201 (5.7%) persons within our cohort tested COVID-19 positive during the one-month follow-up period. [Table 1] Ivermectin prophylaxis uptake was better with increasing age and among males. Out of 331 participants, who had symptoms suggestive of SARS-CoV-2 infection, 200 (60.4%) participants were from the group who have not taken ivermectin prophylaxis. The participants who took ivermectin prophylaxis had a lower risk of getting symptoms suggestive of SARS-CoV-2 infection(6% vs 15%). [Table 2]

The incidence of SARS-CoV-2 infectionwas found lower in the ivermectin prophylaxis group compared to the group without ivermectin (2.0% vs 11.7%). The absolute risk reduction was 9.7%.Participants who had taken two-doses of ivermectin prophylaxis had a lower risk of contracting COVID-19 disease (RR0.18, 95% CI, 0.13-0.25) in the following month after receiving prophylaxis.On adjusting for age, sex, and profession, the single-dose of ivermectin intake was not significant for lowering the risk of (ARR 1.04, 95% CI, 0.69-1.58).However, two-doses of ivermectin prophylaxis had a significantly lower risk (ARR 0.17; 95% CI, 0.12-0.23). Females had a lower risk of contracting COVID-19 diseasecompared to males (ARR 0.70 95% CI, 0.52-0.93). [Table 3]

We estimated the hazard ratio, excluding those who had been diagnosed as COVID-19 positive before the commencement of the study using the Kaplan-Meier method. The probability of SARS-CoV-2 infectionwas 85% lower in those taking two-dose ivermectin at the end of 30 days (HR 0.15; 95% CI, 0.11-0.21). [Figure 1]

Information regarding adverse effects was collected through the existing pharmacovigilance services of the institute, and telephonic follow up. A total of 42 (1.8%) participants reported adverse events following oral ivermectin. All adverse effects were self-limiting and mild in nature, and none required medication or hospitalization. Adverse events were-headache, diarrhoea, nausea, itching, rashes, fatigue, vomiting, dizziness, and abdominal pain. [Table S1]

Discussion

We observed that the HCWs who took ivermectin chemoprophylaxis had an 83% lower risk of contracting COVID-19 disease in the following month compared to those who did not receive the drug. Based on its long history of clinical use, favourable safety profile, and emerging evidence from the in-vitro study, observationalstudy, and open-label RCT, ivermectin was used as a prophylactic agent for COVID-19 disease in our hospital for HCWs and has shown promising results. The adverse effects reported by the subjects were few and fit into the safety profile of this drug.

Ivermectin is a widely available anti-parasitic drug and has been included in the WHO list of essential medicines. The safety of the drug has been established by its large-scale use in the last four decades for various indications such as onchocerciasis, scabies, head lice, and other parasitic infestations such as ascariasis and trichuriasis.[12] Ivermectin has been reported to inhibit the interaction between importin (IMP) α/β1 heterodimer integrase protein, which helps in the nuclear import and propagation of infection

by RNA viruses. It exerts its antiviral activity against a variety of RNA viruses, including West Nile virus, Influenza virus, and Dengue virus.[13]An *in-vitro* study by Caly et al. reported a nearly 5000 fold reduction in the SARS-CoV-2 viral RNA with the use of ivermectin.[5] However, a simulation study has suggested that despite a high lung: plasma concentration ratio, ivermectin would not achieve the required inhibitory concentration in the lungs after a single oral administration at the approved dose and may necessitate much higher doses.[14] Nevertheless, clinical studies have shown that the addition of ivermectin at doses ranging from 150 to 200 µg/kg body weight led to lower mortality and greater clinical improvement in COVID-19 patients. A recent meta-analysis explored its therapeutic potential in COVID-19 patients and reported a significant reduction in all-cause mortality with a pooled odds ratio of 0.53 (95%CI: 0.29 -0.96, p=0.04) with the addition of ivermectin as compared to standard therapy.[15] A recent retrospective cohort study by Rajter JC et al. also demonstrated that ivermectin lowered mortality during treatment of COVID-19.[16]

A randomized open-label clinical trial carried out by Shouman et al. in Egypt showed that prophylactic ivermectin therapy at an average dose of 300 µg/kg body weight in primary contacts of COVID-19 patients led to significantly lower infections (7.4%) compared to controls (58.4%).[7] The half-life of the drug is 12-36 hours following oral administration, and it undergoes hepatic metabolism and is eliminated primarily through the faecal route over 12 days, with less than 1% being eliminated through the renal route. The active metabolites persist in the body for three days.[12] The dose regimen chosen for prophylaxis in our study was thus based on these pharmacokinetic parameters, and the fact that dosage chosen in the clinical trial by Shouman was associated with high clinical efficacy and low rate of adverse events.[7]In our study, we also find that females had a lower risk of SARS-CoV-2 infectioncompared to males. The previous research from India also had similar findings.[17,18]

The strengths of our study are the large sample size, minimal loss to follow-up, and the establishment of temporality. The ideal study design to answer our research question would be a randomized controlled clinical trial. However, due to ethical reasons, we could not choose this design. HCWs who took ivermectin may somehow differ from the HCWs who did not prefer to take the prophylaxis in their behaviour. However, we had a strong institutional policy in place related to COVID-19 appropriate behaviour in the workplace, which may have avoided the possible bias. The major limitation is that we only tested HCWs who either developed symptoms or who were direct or high-risk contacts of positive patients. This was done in keeping with the Government strategy for COVID-19 testing in India. However, this precludes us from including the HCWs who may have been asymptomatic or mildly symptomatic and chose not to get tested. This may be a small number, but the interpretation of our results must also take this factor into account.

We believe that ivermectin is a low-cost prophylaxis that can easily be used in many settings to reduce the burden of the disease until a vaccine is successfully rolled out widely. Further research is required to guide the frequency of chemoprevention, acceptability, and cost-effectiveness in the community setting.

Conclusion

In addition to behaviour prophylaxis, two-doses (300 µg/kg at a gap of 72 hours) of ivermectin chemoprophylaxis reduces COVID-19 disease by 83% among healthcare workers for one month. Ivermectin is safe and may constitute a cost-effective strategy to prevent COVID-19 disease until a vaccine is available for general use. Further research is required to guide the frequency of chemoprevention, acceptability, and cost-effectiveness in the community setting.

Abbreviations

COVID-19 - Coronavirus disease 2019

AIIMS – All India Institute of Medical Sciences

RTPCR – Real-time reverse transcription-polymerase chain reaction

ARR – Adjusted Relative Risk

HCW – Health Care Workers

WHO – World Health Organisation

SD – Standard Deviation

RCT – Randomised Control Trial

RNA – Ribonucleic Acid

Declarations

Ethical consideration

The protocol was approved by the Institutional Ethics Committee of AIIMS Bhubaneswar (T/IM-NF/CM&FM/20/142). Written informed consent was obtained from each participant.

Consent for publication

Written informed consent was obtained from the participants.

Availability of data and materials

The anonymized minimal dataset has been uploaded to the public repository (figshare). The dataset can be accessed at the following link**.** https://doi.org/10.6084/m9.figshare.13663763

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Tables And Panel

Table 1: Characteristic features of participants (n=3532)

Characteristic	Number of participants n (%)
Age (in years)	
Less than 30	1887 (53.4)
30 to 39	1139 (32.3)
40 to 49	358 (10.1)
50 and more	148 (4.2)
Gender	
Male	2389 (67.6)
Female	1143(32.4)
Profession	
Staffs involved in COVID-19 patient care	2567 (72.7)
Administrative staff	492 (13.9)
Students	473 (13.4)
Ivermectin prophylaxis	
No ivermectin prophylaxis	1147 (32.5)
Received Single-dose ivermectin prophylaxis	186 (5.3)
Received double-dose ivermectin prophylaxis	2199 (62.2)
Symptoms suggestive of SARS-CoV-2infection during follow-up	
Present	331 (9.4)
Absent	3201 (90.6)
Follow-up confirmation of COVID-19 by RT-PCR	
Positive	201(5.7)
Negative	3331(94.3)

Table 2: Distribution of participants with ivermectin prophylaxis

	Ivermectin two-dose prophylaxis		
Variables	**Yes**	**No**	**p-value**
Age			
Less than 30	1115 (50.7)	772 (57.9)	<0.001
30 to 39	705 (32.1)	434 (32.6)	
40 to 49	262 (11.9)	96 (7.2)	
50 and more	117 (5.3)	31 (2.3)	
Gender			
Male	1622 (67.9)	767 (32.1)	<0.001
Female	577 (50.5)	566 (49.5)	
Profession			
Staffs involved in COVID-19 patient care	1582 (71.9)	985 (73.9)	0.236
Administrative staff	306 (13.9)	186 (13.9)	
Students	311 (14.2)	162 (12.2)	
Symptoms suggestive of SARS-CoV-2 infection during follow-up			
Positive	131 (6.0)	200 (15.0)	<0.001
Negative	2068 (94.0)	1133 (85.0)	

Table 3: Risk factors for SARS-CoV-2infection

Variables	Total participants	Follow-up COVID-19 positive	Unadjusted RR (95% CI)	P-value	Adjusted RR (95% CI)	P-value
Age						
Less than 30	1887 (53.4)	116 (57.7)	Reference		Reference	
30 to 39	1139 (32.3)	61 (30.3)	0.87 (0.64-1.18)	0.370	0.87 (0.65-2.18)	0.392
40 to 49	358 (10.1)	18 (9.0)	0.82 (0.50-1.33)	0.415	0.95 (0.59-1.54)	0.848
50 and more	148 (4.2)	6 (3.0)	0.66 (0.30-1.47)	0.310	0.85 (0.39-1.89)	0.694
Gender						
Male	2389 (67.6)	138 (68.7)	Reference		Reference	
Female	1143(32.4)	63 (31.3)	0.95 (0.71-1.27)	0.751	**0.70 (0.52-0.93)**	**0.015**
Profession						
Staffs involved in COVID-19 patient care	2567 (72.7)	150 (74.6)	Reference		Reference	
Administrative staff	492 (13.9)	24 (11.9)	0.83 (0.55-1.27)	0.399	0.82 (0.54-1.24)	0.354
Students	473 (13.4)	27 (13.5)	0.98 (0.66-1.45)	0.908	1.09 (0.74-1.61)	0.652
Ivermectin prophylaxis						
No ivermectin prophylaxis	1147 (32.5)	133 (66.2)	Reference		Reference	
Received single-dose ivermectin prophylaxis	186 (5.3)	23 (11.4)	1.07 (0.70-1.61)	0.761	1.04 (0.69-1.58)	0.846
Received two-doses ivermectin prophylaxis	2199 (62.2)	45 (22.4)	**0.18 (0.13-0.25)**	**<0.001**	**0.17 (0.12-0.23)**	**<0.001**

Panel 1: AIIMS Bhubaneswar consensus statement for ivermectin prophylaxis among healthcare workers.

Based on the long history of clinical use, favourable safety profile, and the reportedly promising effect of ivermectin as a prophylactic agent in COVID-19, the expert committee group proposes the following consensus statement:

Suggested prophylaxis for doctors/nurses/staff/students of AIIMS Bhubaneswar with ivermectin*

First Dose:

Ivermectin 300 mcg/kg body weight on Day 1 (Directly Observed) and 4 (72 hours apart).

For 40-60 kg : 15mg, 60-80 kg :18 mg, > 80 kg : 24 mg

Subsequent dose: once a month dose (as above/kg body weight) on every 30th day after the last dose.

Ivermectin should be taken on an empty stomach with water.

*The above schedule will be followed till further guideline/new evidence is available.

*Pregnant women will not be given this drug. Women of childbearing age will be warned not to conceive while on this drug, in case they decide to take the drug.

This consensus statement had been prepared by a team of faculty members from various specialities and discussed and approved in the COVID 19 Working Group meeting on September 11 2020.